

## **REMARKS**

### **Species Election**

The Examiner has maintained the requirement for election of species "in view of the various cognitive disorders to be treated and the number of augmenting agents taught by applicants". Paper No. 20040303, at page 2, lines 4-6.

Applicants traverse for the reasons of record. In particular, Applicants submit that it would not place an undue burden upon the Examiner to search a *class* (genus) of augmenting agents and disorders. A search of the prior art for one member of a *class* of augmenting agents and one member of a *class* of disorders would also identify prior art that is applicable to the other members.

### **Rejection of Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 Under 35 U.S.C. § 103(a)**

The Examiner has maintained the rejection of Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 under 35 U.S.C. § 103(a) as being unpatentable over Takayama *et al.* (U.S. Pat. No. 5,817,670), Katzung (*Basic & Clinical Pharmacology*, page 195 (1995)) and Tully *et al.* (WO96/11270) in view of Calvanio *et al.* (*Neurol. Clin.*, 11(1):25-57 (1993)).

The claims presently being examined relate to ***the treatment or rehabilitation of a cognitive deficit*** associated with stroke by using Applicants' augmented cognitive training method. Applicants' augmented cognitive training method comprises a specific cognitive training protocol and administration of an augmenting agent which enhances CREB pathway function, such as a phosphodiesterase inhibitor. Importantly, the claimed invention ***does not*** relate to the treatment of stroke episodes.

### ***Teachings of the Cited References***

#### **Takayama *et al.***

Takayama *et al.* is cited by the Examiner as teaching that "phosphodiesterase inhibitors are useful in the treatment of stroke". Paper No. 20040303, at page 3, lines 7-8. Although Takayama *et al.* teach the use of phosphodiesterase inhibitors in the treatment of the stroke

episode (column 6, line 4), the reference does not teach or suggest the use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits *associated* with stroke.

Takayama *et al.* do not teach or suggest the use of phosphodiesterase inhibitors in stroke rehabilitation. In addition, Takayama *et al.* do not teach or suggest combining any phosphodiesterase inhibitor treatment with a cognitive training protocol.

#### Katzung

Katzung (page 195) is cited by the Examiner as also teaching that "phosphodiesterase inhibitors are useful in the treatment of stroke". Paper No. 20040303, at page 3, lines 7-8. This characterization of the teachings at page 195 is incorrect. In fact, it is stated at page 195 that "Drugs that inhibit phosphodiesterases, the family of enzymes that inactivate cAMP and cGMP, have long been used in *therapy of heart failure*" (emphasis added). Heart failure is distinct from the stroke episode. Heart failure occurs when the heart is unable to pump blood effectively throughout the body. As a result, some of the blood that is normally pumped out of the heart backs up into the lungs and other parts of the body. In contrast, stroke is a sudden decrease or interruption in blood flow to the brain caused by: (1) the total obstruction of any artery that delivers blood to the brain; (2) rupture of a blood vessel in the brain, followed by hemorrhaging into the brain tissue; or (3) atherosclerosis.

More importantly, Katzung does not teach or suggest the use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke. Katzung does not teach or suggest the use of phosphodiesterase inhibitors in stroke rehabilitation. In addition, Katzung does not teach or suggest combining any phosphodiesterase inhibitor treatment with a cognitive training protocol.

#### Tully *et al.*

Tully *et al.* teach methods of modulating long term memory based on differential regulation of CREB activators and CREB repressors but do not teach or suggest the specific use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke. In addition, Tully *et al.* do not teach or suggest combining any drug treatment with a cognitive training protocol for use in treating cognitive deficits associated with stroke.

Calvanio *et al.*

In Paper No. 9, Calvanio *et al.* was cited as teaching "the benefits of training to stroke patients", specifically that "learning can be accelerated and produce a higher level of outcome" "by detecting and controlling attentional functioning in specific tasks". Paper No. 9, at page 3, lines 18- 20. Calvanio *et al.* discuss various training procedures to alleviate cognitive deficits in stroke survivors but do not teach or suggest combining training with any drug treatment, such as phosphodiesterase inhibitor treatment.

*The Combination of References*

None of the cited references (Takayama *et al.*, Katzung, Tully *et al.*, Calvanio *et al.*), alone or in combination, would have suggested to one of ordinary skill in the art at the time the invention was made, with a reasonable expectation of success, treatment or rehabilitation of a cognitive deficit associated with stroke by using Applicants' augmented cognitive training method. None of the cited references, alone or in combination, would have suggested to one of ordinary skill in the art at the time the invention was made, with a reasonable expectation of success, Applicants' augmented cognitive training method which comprises a specific cognitive training protocol and administration of an augmenting agent which enhances CREB pathway function, such as a phosphodiesterase inhibitor. As discussed above, Takayama *et al.* teach the use of phosphodiesterase inhibitors in the treatment of the stroke episode, but do not teach or suggest the use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke or the combining of phosphodiesterase inhibitor treatment with cognitive training methods. Katzung teaches the use of phosphodiesterase inhibitors in therapy of heart failure, which is distinct from stroke. More importantly, Katzung does not teach or suggest the use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke or the combining of phosphodiesterase inhibitor treatment with cognitive training methods. Tully *et al.* teach methods of modulating long term memory based on differential regulation of CREB activators and CREB repressors, but do not teach or suggest the use of phosphodiesterase inhibitors in the treatment of cognitive deficits associated with stroke or the combining of drug treatment with cognitive training methods. Calvanio *et al.* teach

several cognitive training methods for use in stroke rehabilitation, but do not teach or suggest the combining of training methods with drug treatment, such as phosphodiesterase inhibitor treatment. Accordingly, the cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

In response to Applicants' arguments, the Examiner contends that "it was well known in the art that in the treatment of stroke, rehabilitation of the individual suffering from stroke should begin therapy as early as possible, even when the patient is on intravenous medication". Paper No. 20040303, at page 2, lines 16-20. In support of this position, the Examiner cites the Merck Manual "as extrinsic evidence of the ordinary protocol in treating a stroke patient", arguing that "[s]uch a patient would be on medication as soon as possible and be given therapy as early as possible". Paper No. 20040303, at page 3, lines 11-12. The Examiner also states that "[a]s the claims are drafted the patient is an individual suffering from stroke". Paper No. 20040303, at page 3, line 10.

The claims presently being examined relate to use of Applicants' augmented cognitive training method in *the treatment or rehabilitation of a cognitive deficit* associated with stroke. Applicants' augmented cognitive training method comprises a specific cognitive training protocol and administration of an augmenting agent which enhances CREB pathway function. The claimed invention *does not* relate to the treatment of the stroke episode.

Respectfully, the basis in the Merck Manual (pages 1454-1456) relied upon by the Examiner for the desirability of the proposed combination of references would not have led one of ordinary skill in the art to combine the teachings of Takayama *et al.*, Katzung, Tully *et al.* and Calvanio *et al.* In particular, the Merck Manual teaches at page 1455 that passive exercise, particularly of paralyzed limbs, and breathing exercises (referred to by the Examiner in the Office Action) should be started early in the treatment of heart failure, arrhythmias, severe hypertension and intercurrent respiratory infection. The Merck Manual also teaches at page 1455 that treatments to minimize brain damage from acute stroke must begin very soon after stroke onset. With regard to rehabilitation and aftercare, the Merck Manual teaches at pages 1455 to 1456 early, repeated appraisals of a stroke patient's status to promote design of a remedial program; early treatment, continuing encouragement, and orientation toward the outside environment to

influence rehabilitation; occupational and physical therapy that emphasizes using affected limbs and achieving proficiency in eating, dressing, toilet functions, and other basic needs; reassurance and understanding to treat mood changes. The Merck Manual does not teach or suggest the use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke. The Merck Manual also does not teach or suggest combining any phosphodiesterase inhibitor treatment with a cognitive training protocol for the purpose of treating or rehabilitating cognitive deficits associated with stroke.

Accordingly, this rejection is improper because the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The only document of record which suggests the desirability of the proposed combination is Applicants' specification. However, the use of the present specification as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight.

Even assuming, *arguendo*, that the basis in the Merck Manual (pages 1454-1456) relied upon by the Examiner for the desirability of the proposed combination of references would have motivated one of ordinary skill in the art to combine the teachings of Takayama *et al.*, Katzung, Tully *et al.* and Calvanio *et al.*, as discussed above, the cited combination of references would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

Reconsideration and withdrawal of this rejection Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 under 35 U.S.C. § 103(a) are respectfully requested.

Rejection of Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-1-6 Under 35 U.S.C. § 103(a)

Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Christensen IV *et al.* (U.S. Patent No. 5,547,979) in view of the Merck Manual. In particular, the Examiner argues that Christensen IV *et al.* teach the use of rolipram in a method of treating stroke and the Merck Manual provides the skilled artisan with the motivation to administer the medication in conjunction with a training protocol.

Applicants respectfully disagree that the claimed invention is obvious in view of the cited references.

First, the claimed invention ***does not*** relate to the treatment of the stroke episode. Rather, the claims presently being examined relate to use of Applicants' augmented cognitive training method in ***the treatment or rehabilitation of a cognitive deficit*** associated with stroke. Applicants' augmented cognitive training method comprises a specific cognitive training protocol and administration of an augmenting agent which enhances CREB pathway function.

Second, Christensen IV *et al.* do not teach or suggest the use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke. Christensen IV *et al.* do not teach or suggest the use of phosphodiesterase inhibitors in stroke rehabilitation. As the Examiner acknowledges, Christensen IV *et al.* also do not teach or suggest combining any phosphodiesterase inhibitor treatment with a cognitive training protocol.

Third, the basis in the Merck Manual (pages 1454-1456) relied upon by the Examiner for the desirability of the proposed combination of references would not have led one of ordinary skill in the art to combine the teachings of Christensen IV *et al.* with the teachings in the cited pages of the Merck Manual. In particular, it is noted that the Merck Manual teaches at page 1455 that passive exercise, particularly of paralyzed limbs, and breathing exercises (referred to by the Examiner in the Office Action) should be started early in the treatment of heart failure, arrhythmias, severe hypertension and intercurrent respiratory infection. The Merck Manual also teaches at page 1455 that treatments to minimize brain damage from acute stroke must begin very soon after stroke onset. With regard to rehabilitation and aftercare, it is noted that at pages 1455 and 1456, the Merck Manual teaches early, repeated appraisals of a stroke patient's status to promote design of a remedial program; early treatment, continuing encouragement, and orientation toward the outside environment to influence rehabilitation; occupational and physical therapy that emphasizes using affected limbs and achieving proficiency in eating, dressing, toilet functions, and other basic needs; reassurance and understanding to treat mood changes. The Merck Manual does not teach or suggest the use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke. The Merck Manual also does not teach or suggest combining any phosphodiesterase inhibitor treatment with a cognitive training protocol for the purpose of treating or rehabilitating cognitive deficits associated with stroke.

Even assuming, *arguendo*, that the basis in the Merck Manual (pages 1454-1456) relied upon by the Examiner for the desirability of the proposed combination of references would have motivated one of ordinary skill in the art to combine the teachings of Christensen IV *et al.* with the teachings in the cited pages of the Merck Manual, the cited combination of references would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success. As indicated above, neither the Christensen IV *et al.* reference nor the Merck Manual teaches or suggests the use of phosphodiesterase inhibitors in the treatment or rehabilitation of cognitive deficits associated with stroke or the combining any phosphodiesterase inhibitor treatment with a cognitive training protocol for the purpose of treating or rehabilitating cognitive deficits associated with stroke.

Reconsideration and withdrawal of this rejection Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 under 35 U.S.C. § 103(a) are respectfully requested.

Rejection of Claims 97 and 106 Under 35 U.S.C. § 112, First Paragraph

Claims 97 and 106 have been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification "while being enabling for the compounds rolipram and iso-buto-metho-xanthine, does not reasonably provide enablement for 'a phosphodiesterase as an augmenting agent' the generic language of claim 97 and 106". Paper No. 20040303, at page 5, lines 6-9. Applicants respectfully disagree with this assessment.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

The specification teaches an augmented cognitive training method which comprises a specific cognitive training protocol and administration of an augmenting agent which enhances CREB pathway function. The specification teaches that this combination can improve the

efficiency of existing cognitive training protocols because the combination can augment cognitive training by reducing the number of training sessions required to yield a performance gain relative to that obtained with cognitive training alone or by requiring shorter or no rest intervals between training sessions to yield a performance gain (see, e.g., page 2, line 27 to page 3, line 3). The specification also teaches that this combination can improve the efficiency of existing cognitive training protocols because the combination can augment cognitive training by reducing the duration and/or number of training sessions required for the induction in a specific neuronal circuit(s) of a pattern of neuronal activity or by reducing the duration and/or number of training sessions or underlying pattern of neuronal activity required to induce CREB-dependent long-term structural/function change among synaptic connections of the neuronal circuit (see, e.g., page 3, lines 3-8).

In a particular embodiment, the specification teaches use of Applicants' augmented cognitive training method in the treatment or rehabilitation of a cognitive deficit associated with stroke. More specifically, the specification teaches use of Applicants' augmented cognitive training method in stroke rehabilitation (see, e.g., page 3, lines 23-28).

The specification teaches that augmenting agents are CREB pathway-enhancing drugs (see, e.g., page 5, lines 1-2) which are able to enhance or improve CREB-dependent gene expression (see, e.g., page 11, lines 1-2). Specific examples of augmenting agents provided in the specification include phosphodiesterase inhibitors (see, e.g., page 18, lines 26-28). Specific examples of phosphodiesterase inhibitors provided in the specification include rolipram and isobuto-metho-xanthine (IBMX) (see, e.g., page 18, lines 26-28). One skilled in the art would reasonably expect, contrary evidence to the contrary, that other phosphodiesterase inhibitors (i.e., in addition to rolipram and IBMX), can be successfully employed in Applicants' augmented cognitive training method. One skilled in the art would reasonably expect that Applicants' augmented cognitive training method employing phosphodiesterase inhibitors, other than rolipram and IBMX, can be successfully used, for example, in the treatment of a cognitive deficit associated with stroke (i.e., in stroke rehabilitation). That is, one skilled in the art would accept the assertions in the specification as true and enabling. No evidence has been provided as to why the teachings in the specification with regard to rolipram and IBMX cannot be correlated to other phosphodiesterase inhibitors.



Indeed, a study has been conducted since the filing of the application which demonstrates that the phosphodiesterase inhibitor HT0712 can be successfully employed in Applicants' augmented cognitive training method and used in the treatment of a cognitive deficit associated with stroke (i.e., in stroke rehabilitation). The results of this study provide further evidence that one skilled in the art would expect that other phosphodiesterase inhibitors (i.e., phosphodiesterase inhibitors other than rolipram and IBMX) can be successfully employed in Applicants' augmented cognitive training method and used in the treatment of a cognitive deficit associated with stroke. A description and discussion of this study is provided in the Exhibit attached hereto. A Declaration under 37 C.F.R. § 1.132 describing the results of this study is being prepared and will be filed as soon as it is received from the Declarant.

Reconsideration and withdrawal of the rejection Claims 97 and 106 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

### CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

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